Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Applicants have amended the title to better describe the claimed invention. Claims 119-138 are pending in this application and are rejected on various grounds. All pending claims have been amended to remove references to "Figures". Claims 119-123 have been amended with the functional recitation "wherein, said encoded polypeptide is an immunosuppressor," support for which is found in the instant specification in Example 155. Further, new claims 138-143 which recite the functional recitation "wherein, said encoded polypeptide induces chondrocyte redifferentiation" have been added, support for which is also found in the instant specification in Example 159. Claims 127-128 and 132-134 have been canceled without prejudice of disclaimer. Accordingly, Claims 119-126, 129-131, 135-143 are currently pending in this application and rejections to these claims are respectfully traversed.

Specification

A and B. The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections. Further, any minor errors have been amended.

Accordingly, Applicants believe that all objections to the specification has been overcome.

Claim Rejections – 35 U.S.C. § 101

Claims 137 was rejected under 35 U.S.C. §101, for not sufficiently distinguishing over cells that exist naturally.

The claim has been amended to recite "isolated" as recommended by the Examiner to overcome this rejection and accordingly this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 119-138 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that the protein identified as PRO1159 is a soluble protein and

is not disclosed as being expressed on a cell surface and accordingly, claims that recite an "extracellular domain" is indefinite as the art does not recognize soluble proteins as having such domains. The Examiner further rejects Claim 132-134 as indefinite for reciting "hybridizes." Applicants respectfully traverse these rejections.

Without acquiescing to the propriety of this rejection and without limitations to pursuing this subject matter in future applications, merely to expedite prosecution in this case, Applicants have canceled references to "the extracellular domain" in the pending claims and further, have canceled claims 132-134 without prejudice or disclaimer. Accordingly, this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph -written description

10. Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

As will be discussed below, specific utilities have now been asserted for the presently pending claims that recite functional recitations "wherein said encoded polypeptide is an immunosuppressor" and "wherein said encoded polypeptide induces chondrocyte redifferentiation." Since the claims are drawn to a genus of nucleotides defined both by sequence and functional identity, it would have been obvious to one skilled in the art at the effective priority date, in view of Applicant's possession of the nucleic acid of SEQ ID NO:376 and the PRO1159 (SEQ ID NO:377), that the Applicant possessed these obvious variations and adaptations of SEQ ID NO:377 at the time of filing.

Hence, Applicants request that the present rejection be reconsidered and withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph -enablement

11. Claims 119-123, 131-138 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner objected to the disclosure for lack of evidence for the claimed biological materials required for practicing the claimed invention, for allegedly, not being

known and readily available to the public or obtainable by a repeatable method set forth in the specification.

Applicants submit that the specification contains information regarding ATCC accession no. 203092 which was deposited August 4, 1998 (also called DNA 60627-1508) on page 565, line 35. This deposit was made under the provisions of the Budapest Treaty. Applicants further submit amendments to the specification regarding the ATCC deposit incorporating the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Accordingly, Applicants request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 112, first paragraph-enablement

12. Claims 119-123 and 132-138 are rejected under 35 U.S.C. §112, first paragraph for failing to adequately teach how to make and/or use the instant invention. The Examiner acknowledges that the specification discloses that the PRO1159 polypeptide was positive for the chondrocyte re-differentiation assay (Assay 110, page 530) but asserts that the specification does not teach an activity for the polypeptide or any active regions and therefore concludes that one would not know if the polypeptide with the claimed homology would function as a polypeptide of PRO1159. For the reasons outlined below, Applicants respectfully disagree.

Initially, Applicants submit that the instant claims do not have utility based on "homology" and hence the articles Burgess *et al.*, Lazar *et al.*, Schwartz *et al.* and Lin *et al.* are not appropriate citations in this instance. Instead, utility is based on positive results of obtained in the 'inhibition of the mixed lymphocyte reaction (MLR)' assay (Example 155) and the 'chondrocyte redifferentiation' assay (Example 159) and these functional recitations are now recited in the instantly amended claims.

PRO1159 polypeptides have utility as immunosuppressors

Without acquiescing to the propriety of this rejection, but solely in the interest of expediting prosecution in this case, Applicants submit a declaration with supportive references from the art to show that PRO1159 polypeptides have immunosuppressive activity based on the positive results obtained in the "inhibition of MLR assay".

Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology and co-inventor of the present application, to show that there are specific immune stimulant utilities for compounds identified by an MLR assay. The Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Further, Dr. Fong's declaration clearly states that:

> "Some PRO polypeptides do the reverse, and give inhibition of T-cell proliferation in the MLR assay. It is my considered scientific opinion that a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases".

Accordingly, the positive results obtained in this assay clearly establish the stated utility for the polypeptides claimed as immunosuppressors. By the foregoing arguments and supportive evidence, Applicants have established that the MLR reaction is a generally recognized assay to assess immunoinhibitory as well as immunostimulatory activity. Thus, the PRO1159 polypeptides have immunosuppressive uses, for example, in the treatment of graft rejections, autoimmune diseases, etc.

Since the legal standard accepts *in vitro* as acceptable utility and the data is "reasonably correlated" to the pharmacological utility based on the discussions above, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art.

PRO1159 polypeptides also have utility based on results in chondrocyte redifferentiation assay

Applicants further rely on the chondrocyte redifferentiation assay (Example 159) for support of patentable utility.

It was well known at the effective filing date of the present application that chondrocytes play a key role in the synthesis and maintenance of the articular cartilage, which in turn is essential to normal joint function. Unfortunately, compared to many other tissues, articular

cartilage essentially lacks the ability to regenerate following injury. One way of achieving cartilage repair, for example in osteoarthritis, is to harvest human articular chrondrocytes (HACs) from non-affected, healthy areas of the joint to be repaired. The HACs are subsequently grown in monolayer cell culture in order to produce sufficient amount of cells to fill the articular defect. Chondrocytes found in healthy joints have a round shape, and express high levels of extracellular matrix molecules, such as aggrecan, type II collagen, and link protein. In contrast, monolayer cultures of chondrocytes produce dedifferentiated fibroblast-like structures, similar to those found in the cartilage of aging and arthritic joints. (See, e.g. Zhang et al., *Experimental Cell Research* 263:33-42 (2001) – copy enclosed). Accordingly, agents that are capable of inducing chondrocyte proliferation and redifferentiation, as evidenced by proper growth and differentiation of chrondrocytes in monolayer cell cultures, can be used in the treatment of joint diseases using a tissue engineering approach (See, e.g. Schnabel et al., Osteoarthritis and Cartilage, 10(1):62-70 (2002) – copy enclosed). In addition, molecules capable of inducing chondrocyte proliferation and/or redifferentiation are promising drug candidates to repair aging or arthritic joints, for example, in joints where the chondrocytes have been dedifferentiated.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Applicants refer to the statement in Example 159, the description of the chondrocyte redifferentiation assay that "A positive result in the assay is obtained when the fluorescence of the PRO polypeptide treated sample is more like that of the positive control than the negative control." Fluorescence determination wherein the readout is compared to controls is well known in the art. Thus, these indica are truly determinative of the proliferation of chondrocyte cells.

Applicants respectfully submit that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1159 polypeptide and its encoding nucleic acids. In addition, the instant claims, as amended, (and, as a consequence, those claims dependent from the same) now recite the functional recitation, namely that the encoded polypeptide either is an immunosuppressor or induces chondrocyte re-differentiation.

Accordingly, Applicants respectfully submit that it would not require undue experimentation for one of skill in the art to apply the teachings of the present disclosure so as to practice the invention of the instant claims (and, as a consequence, those claims dependent from the same).

In view of the foregoing arguments and submitted evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C.§112, first paragraph.

Priority

Applicants rely on the 'inhibition of the mixed lymphocyte reaction' assay (Example 155) for patentable utility of subject matter relating to claims 119-123 in this case. This utility was first disclosed in International Application PCT/US00/05841, filed March 2, 2000, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **March 2, 2000** based on the results of the "inhibition of MLR" assay.

Further, Applicants rely on the 'chondrocyte redifferentiation' assay (Example 159) for patentable utility of subject matter relating to new claims 132-136 in this case. This utility was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **March 30, 2000** based on results of the 'chondrocyte redifferentiation' assay.

Claim Rejections – 35 USC § 102

14. Claims 132-133 are rejected under 35 U.S.C. §102(b) as being anticipated by the 1991 Boehringer Mannheim Catalog, page 557.

15. Claims 132-134 are rejected under 35 U.S.C. §102(e) as being anticipated by Studier (U.S. Patent 5,407,799).

In view of the cancellation of claims 132-134, these rejections are moot and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C66). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 16, 2004

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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